National Institute of Allergy and Infectious Diseases
Division of Acquired Immunodeficiency Syndrome

Meeting of the
AIDS Research Advisory Committee

January 26, 2004
Natcher Building, Conference Rooms E1-E2
NIH Campus, Bethesda, Maryland

The AIDS Research Advisory Committee (ARAC) of the National Advisory Allergy and Infectious Diseases Council met on January 26, 2004 at the Natcher Building on the National Institutes of Health (NIH) campus in Bethesda, Maryland.

Dr. Holmes chaired the meeting, which was open to the public. ARAC members in attendance were: Drs. Balfour, Jackson, Kanki, Lewis, Marx, Ruff, Ruprecht, and Thielman; Office of AIDS Research Advisory Council liaison Dr. Haase; and *ex officio* member Dr. Deyton.

Also present were DAIDS staff Drs. Dieffenbach, Fishbein, Johnston, Kagan, Lehrman, and Tramont, and Mr. Montoya and Mr. Murguia. Ms. Siskind was Executive Secretary.

Dr. Holmes convened the meeting at 1:00 pm.

Director's Report – Dr. Tramont

Dr. Tramont introduced Dr. Ruth Ruprecht and Dr. Nathan M. Thielman as the newest members of the ARAC. Dr. Deborah Birx will formally join the committee as an *ex officio* member given the growing collaboration with the Department of Defense.

Budget Update: Congress recently passed an omnibus appropriations bill containing the budget for NIH, though the President has not yet signed it. NIAID has grown by 15.4% over the last year to $4.3 billion to become the second largest institute at NIH. That position is fueled by increases in biodefense research, which is increasing by 38%, while other areas are essentially flat-funded. The NIH AIDS budget is roughly $2.8 billion, of which approximately half goes to NIAID. The remainder is divided among 22 other institutes and centers.

The AIDS vaccine budget totals $456 million. The pipeline of candidates advancing toward trials is increasing while the overall AIDS budget is not. Dr. Tramont presented estimates of what future AIDS vaccine budgets are likely to be and his projections of what the demand will be. He projected potential shortfalls that will continue to increase over the next 5 years due to the costs associated with increased product development and clinical trials capacity.

Vaccine Clinical Trials Update: DAIDS established a consultation group to review and analyze data from the VaxGen Phase III trial soon after the initial results were released. The AIDS Vaccine Research Working Group (AVRWG) was briefed on the trial in September. The results of the consultation group's review will be presented at the Conference on Retroviruses and Opportunistic Infections in February and again at the National African American AIDS Conference in March.

A phase III HIV vaccine trial in Thailand is being conducted by DAIDS in collaboration with the Department of Defense (DoD). DAIDS is primarily responsible for the science while the DoD has retained operational responsibility. The AIDS Vaccine Research Working Group discussed the trial at their meeting in January 2004 and will be making recommendations on additional research that might enhance the value of the trial. DAIDS will be publishing a response to the letter that *Science* published from 22 leading researchers urging that the trial be halted.

Networks: Dr. Tramont reviewed the DAIDS mission statement and noted that approximately 25% of the DAIDS budget goes to unsolicited grants, primarily through R01s. Approximately 75% of the solicited clinical program, or ~$400 million, is channeled through the network structures. He said that the present structure has been effective but is not optimal for pursuing a growing international research agenda. This and the fact that the clinical research networks were up for renewal, led DAIDS to rethink the organization and structure of the clinical research effort.

Framework for Defining Guiding Principles for DAIDS Clinical Research Networks – Dr. Kagan

Dr. Kagan reviewed the consultative process that has taken place to discuss the clinical research effort. He identified two options that were considered for the future, namely to reconstruct the networks or evolve them into structures more suitable for current and future research challenges. The consensus was the latter course of action – to adapt the networks to better address changing scientific priorities; changing demographics of the disease at home and abroad; changing partners; changing oversight and regulatory bodies; and changing fiscal constraints. By evolving and adapting the networks, it is believed that the research could continue to move forward.

Guiding Principles for Evolving the Networks:
Key issues were identified to help guide the development of the future clinical research program, including:

- Ensure that the research programs/activities match the highest priorities for the domestic and international research agendas.

- Integrate HIV/AIDS prevention and treatment research for the best clinical science, particularly in those parts of the world that do not have a health care infrastructure.

- Maximize scientific opportunities through coordinated research; go beyond an exchange of information. Ensure that different groups are aware of each other's research plans at an early enough stage to integrate research activities.

- Increase efficiencies and resource sharing, where it makes sense, and to not duplicate facilities unnecessarily.

- Build and sustain clinical research capacity in resource poor settings.

- Partner with other agencies and organizations with complementary strengths to build upon DAIDS' capabilities.

Implementing this will require:

- Leadership and coordination, including increased accountability of network leadership on these issues
- Building infrastructure at international sites
- Coordinating and integrating data through standardization of procedures, assays, and data management to the greatest extent possible
- Shared and standardized training for common needs
- Coordination, standardization, and where advisable centralization of administrative procedures to acquire goods and services to support research activity

Some specific objectives discussed involved:

- Cross-group leadership and the need for increased accountability and coordination
- Pluripotent international clinical sites
- Shared laboratory resources and protocols
- Common data entry interfaces and data elements
- Shared/standardized training
- Increased interaction
- Coordinated product acquisition, distribution and provision
- Increased efficiency

After reviewing each of these guiding principles in greater detail, Dr. Kagan reminded the committee that DAIDS will be awarding the HIV clinical management support contract (a CRO-like mechanism) in FY 2005. It will be an essential part of reorganizing the clinical research effort and will help build capacity at international sites. He also acknowledged that as part of this reorganization, DAIDS is considering opening up core labs and other network resources to non-network investigators under conditions that have not yet been defined.

Discussion:

1. **Network vs. non-network research:** Several questions were raised concerning the need for directed programs as compared to other competitively funded research and the value/need for single site vs. multi-national research. It was noted that most of the important discoveries in HIV prevention internationally have been made at a single site, or at most within a single country.

   In response, DAIDS staff noted that the individual investigator (non-network) model is not useful for the product development required for creating HIV vaccines and microbicides. Intensive studies do not generally require a network because they use small numbers of patients. However, with some rare exceptions, a network is the only way to collect sufficient patients to power HIV vaccine and microbicide trials, which require large numbers of participants. It was also noted that comparative therapeutic trials that the pharmaceutical industry will not support, could be considered the government's obligation. These types of studies require the resources of a network.

   In addition, the challenges of site development in resource poor settings are formidable. There are efficiencies in having that knowledge remain on site and within a network rather than have to recreate that structure for each trial.

2. **"Center" Model:** The "center" approach, which brings in other disciplines, was discussed as one potential model. Strong leadership was identified as a key element for the success of this approach.

   After discussing the concept of domestic centers that would integrate various aspects of AIDS research, such as malignancies, hepatitis coinfections, DAIDS described the model used for the 19 Centers for AIDS Research. The CFARS have some degree of local control, and are generally integrated within a university. However, the networks that use the site often provide the trial protocols. DAIDS would like to broaden the interactions so that a site can serve more than one network in innovative ways. This may encourage development of more local autonomy within the networks and may introduce "new blood" (e.g., young investigators) into the network system. The CFARS are now on a rolling application schedule and there is a set turnover with each cycle.

3. **Resources for Non-Network Investigators/Shared Resources:** The Immune-Tolerance Network (ITN) was mentioned as one model that provides core support at multiple sites and allows both network and non-network investigators access to resources. The ITN fosters the integration of research on diseases that share common biological processes through the use of a common network. The scale of the DAIDS-funded networks, however, is significantly bigger and the networks have to address issues dealing with infrastructure development in resource poor settings, which the ITN does not.

It was agreed that opening up core laboratories and other support resources for "non-network" investigators could lead to faster translation of basic discovery into clinical models. The standardization of operating procedures, assays, and data management are important aspects of this.

Draft Concepts of DAIDS Clinical Research Networks – Dr. Kagan

Dr. Kagan presented the draft concept for the clinical research networks and outlined the vision of a prototypical network structure. The proposed model would integrate prevention and treatment research to the extent possible. It would also encourage that pediatric and adult research be examined to determine how to achieve better integration. Although domestic and international sites would continue to work together collaboratively within networks, there would be a separate application and funding process for domestic and international sites. The goal is to integrate HIV clinical research and to encourage new thinking to ensure that the research is not conducted in isolation.

One element of the plan is that a core level of funding would be provided to all sites to sustain a base level of functioning (yet to be defined). This would allow DAIDS to make a higher proportion of funds for clinical research networks available to the leadership groups for them to conduct clinical research in response to changing scientific priorities.

Currently, the majority of DAIDS-affiliated international sites have been formed through collaborations with US investigators who are members of networks, and they are often funded through sub-grants from the US institution. The new structure would allow international sites to apply directly to NIAID for core funding for prevention research, treatment research, or both. This is intended to increase the autonomy of the international investigators.

DAIDS said that the networks will be responsible for oversight of sites in situations where there are linkages between the sites and networks. Management contracts will be responsible for building capacity at sites in lesser stages of development. Sites will be evaluated by measures appropriate to their capability.

Questions that emerged during discussion focused on the following:

1. **Formulation of the RFA:** The committee suggested that the scientific objectives be delineated in the RFA so that the leadership groups can be focused and so that new research groups are clear about the scientific goals and priorities and the future direction of NIAID. The significant challenge of reviewing applications was also discussed.

2. **International Sites:** There were a number of questions concerning the establishment of and application process for international sites. It was questioned whether or not there were specific goals for sites with mid-level capacity, such as India, Brazil, or the former Soviet states, and how sites in resource poor developing countries would be evaluated against more established sites in developed countries. There was also

concern that by eliminating the funding link between domestic and international sites, the new structure would sever the peer-to-peer relationships between international sites and domestic institutions.

DAIDS pointed out that it is seeking the best science in both the developed and developing world. In addition, DAIDS felt that the proposed structure would strengthen the independent funding base of international investigators, thereby increasing their status as peers with their US colleagues.

3. **Training:** In recognition of the need to attract new investigators to the field, DAIDS will strengthen training programs in conjunction with the networks, particularly to build capacity at international sites in resource poor developing countries.

Public Comment

Jody Black, National Cancer Institute – Dr. Black asked about motivation and incentives for collaboration with other NIH institutes for both domestic and international research. DAIDS acknowledged that incentives for collaboration would need to build into funding plans.

Michael Marco, AACTG International Operations: Drawing from his experience working with 12 international sites, Mr. Marco emphasized the need for communicating with the international sites as the recompetition proceeds. He thought that some of the international sites fear what may happen in the process and don't want to loose the scientific relationships they have established.

He also stated that the partnerships with CDC and USAID were not satisfactory. DAIDS recognized that working across agencies is difficult, but PAVE (the Partnership for AIDS Vaccine Evaluation) has made tremendous progress.

Gary Gale, PACTG Community Group: Mr. Gale spoke to the special needs of children with HIV and did not want their research needs to be lost in this process. He urged greater integration between institutes, particularly mental health, as well as increased studies of affordable, alternative medicines; and better communication with trial participants about study results.

Yvette Delph, Director AACTG Operations Center: Ms. Delph was concerned with funding of both domestic and international sites and urged that funding be more closely linked to site performance. She also suggested creating "a two-tiered" ranking of international sites so that less developed sites are not expected to compete directly against well-established ones.

She applauded efforts to increase site independence, but said not all sites are capable of such independence because they lack sufficient administrative capabilities and/or political and societal pressures impact their management capabilities. Ms. Delph also

recommended that the RFA include international researchers as part of the leadership group and that this be made one of the criteria for selection.

Mark Mishkin, Regulatory Compliance Center: Mr. Mishkin said that without incentives and milestones, investigators and sites tend to spread themselves too thin in pursuit of funding.

Carol Treston, Director, PACTG Operations Center: Ms. Treston urged the DAIDS to be as specific as possible in the RFA, outlining scientific plans and priorities. She also noted that there is a limit to the capacity of administering these programs and the transition from the current to a new structure will demand new resources. She reiterated that there are capable researchers in developing nations but reminded DAIDS that many of them are in the middle of rolling out the introduction of antiretroviral therapy programs, which may hamper their ability to prepare competitive applications.

Judith Feinberg, MD: Dr. Feinberg expressed concern about whether novel research would be given adequate attention. She questioned how the ideas would be channeled from investigators at the sites to the leadership group and how parochial interests would be balanced against innovative, higher risk ideas.

Dr. Holmes summarized key points of the meeting and made the following recommendations to DAIDS.

- Further clarify the role of network and non-network research in the DAIDS portfolio.
- Explore NIAID's role in relation to PEPFAR, particularly in terms of operational research needs and the potential for additional funding.
- Explicitly delineate the goals and objectives DAIDS has identified in the RFA to ensure responsiveness of the applications.
- Continue to solicit input from individual ARAC members as needed and with other Institutes and Centers.
- Utilize ARAC's preliminary concept review process to facilitate concept review and discussions at the next meeting.

The meeting adjourned at 6:00 p.m.